

IN THE UNITED STATES PATENT OFFICE

In re Mathew LAMMATTEO, M.D.,
"Premenstrual Dysphoric Disorder
Medication"

Serial No. 10/840,131
Filed 6 May 2004

RULE 132 DECLARATION

I, Mathew LAMMATTEO, M.D., do hereby swear as follows:

- 1) I received a Bachelor's of Science in 1981 from University of Maine, Orono, Maine. I received a Doctoral degree in Medicine in 1985 from Ross University School of Medicine, Dominica, West Indies.
- 2) I am Certified as Fellow of the American College of Obstetrics and Gynecology ("FACOG") Fellow of the American College of Surgeons ("FACS").
- 3) I therefore respectfully believe that I am one of skill in the art.
- 4) I have reviewed the art of record in this case, including Robert G. BELL *et al.*, *Oral contraceptives To Prevent Pregnancy*, U.S. Patent Publication No. 2003/0139381, J. STUDD *et al.*, *Transdermal Estrogens for the Treatment of Premenstrual Syndrome*, in PROC. PLENARY SESS. 8TH WORLD CONG. GYNECOLOG ENDOCRINOL. (December 2000); and Ellen W. FREEMAN *et al.*, *Differential Response to Antidepressants*, 56 ARCH. GEN. PSYCHIAT. 932 (Oct. 1999).

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5) I have also reviewed the OFFICE ACTION dated 11 October 2005. I respectfully disagree with certain of the factual assumptions relied on by the OFFICE ACTION.

6) The OFFICE ACTION alleges that my claimed invention is anticipated by Stephen BELL *et al.*, claim no. 42 and its depending claim nos. 48 and 69. Claim no. 42 reads:

42. A kit to diminish premenstrual symptoms consisting of: (a) tablets comprising estrogen and progestin, and (b) tablets comprising estrogen and an antidepressant.

One of skill in the art would read this to teach two kinds of tablets.

7) The first kind of tablet is a tablet containing estrogen and progesterone. This kind of tablet is a conventional contraceptive combination which is known in the prior art. I do not intend my claims to cover this kind of simple contraceptive tablet. I also respectfully believe that one of skill in the art would not read my claims to cover this kind of simple contraceptive tablet.

8) The second kind of tablet taught by BELL *et al.* is a tablet containing estrogen and an antidepressant. I do not intend my claims to cover this kind of two-component tablet. To the contrary, my independent claim 1 describes a three-component tablet, including estrogen and an antidepressant, together with a third component — progesterone. I therefore respectfully believe that one of skill in the art would not read my claims to cover BELL *et al.*'s two-component tablet.

9) Furthermore, one of skill in the art would read BELL *et al.* to teach away from my claimed three-part combination. This is because where a clinical scientist believes that various pharmaceutical combinations are advantageous (or at least are not harmful), it would be expected that the scientist would say so. Where such a suggestion to modify

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does not appear in the reference at issue, one of skill in the art could reasonably infer that the author of the reference suspects that such combination(s) may have adverse drug interactions or other side effects.

10) In the immediate case, BELL is quite specific in teaching tablets with only two components. BELL is pointedly silent on the desirability of my claimed three-part combination. Because BELL is quite specific in teaching a two-component tablet, and is silent on the desirability of a three-part combination, one of skill in the art would read BELL to imply that the claimed three part combination is undesirable and may precipitate adverse drug interactions.

11) J. STUDD *et al.*, *Transdermal Estrogens for the Treatment of Premenstrual Syndrome*, in PROC. PLENARY SESS. 8TH WORLD CONG. GYNECOLOG. ENDOCRINOL. (December 2000) surveys the use of transdermal estrogens for the treatment of premenstrual syndrome. STUDD at page 84 (citations omitted) says:

"These patients, of course, were also given 7-13 days of oral progestogen per month to prevent endometrial hyperplasia and irregular bleeding. Subsequently, a placebo-controlled trial of cyclical norethisterone in hysterectomized women reproduced the typical symptoms of PMS. ... It is common for progestogens to cause PMS-like symptoms (Figure 2), in the same way that endogenous cyclical progesterone is the probable cause of PMS."

STUDD thus teaches that progesterone does not *cure* PMS *progesterone causes PMS*. (STUDD thus confirms the summary of the prior art which I provided in my patent Specification.)

12) Because STUDD teaches that progesterone causes PMS, one of skill in the art would read STUDD to teach away from combining progesterone with the antidepressant PMS therapy taught by FREEDMAN *et al.*

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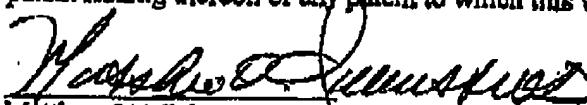
- 13) STUDD teaches that progesterone causes PMS. One of skill in the art would therefore read STUDD to teach a reasonable expectation of not success, but *failure*.
- 14) I have tested my claimed invention and have found that it is both safe and effective. I attach here as Exhibit No. 1 a three page list of the various pharmaceuticals that I have tested in various combinations in patients suffering from premenstrual Dysphoric disorder.
- 15) I attach here as Exhibit No. 2 a summary of my clinical results achieved for several dozen patients tested for the combination therapies described in Exhibit No. 2. To preserve patient confidentiality, I have listed each patient not by name, but by a two-letter code (e.g., DM, BM, LM) and the patient's age.
- 16) As shown in the "Outcomes" column of Exhibit No. 2, approximately 90% of the patients listed here demonstrated a positive clinical outcome. My results would not have been expected by one of skill in the art at the time I made my invention.
- 17) There is a nexus between this evidence and the pending patent claims, because this evidence would be considered by one of skill in the art to have probative value in showing the pending patent claims are enabled and are non-obvious in light of the contrary teachings of the art of record.
- 18) I therefore respectfully believe that my pending claims are not obvious in light of the prior art of record.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are

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punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon or any patent to which this verified statement is directed.


Matthew LAMMATTEO, M.D.

Dated as of Wednesday, December 28, 2005

SDAL18Line Medical 10,840,131 R.132 Declaration (Dec, 2004).doc

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The drugs that were used for the list of patients to follow consisted of a combination of one or more of the following:

ORAL CONTRACEPTIVES

Orthotriptyl Lo	Norgestimate Ethinyl Estradiol (EE)
Ovcon 1/35	Norethindrone .4mg Ethinyl Estradiol .035mg
Ovcon 1/50	Norethindrone .4mg Ethinyl Estradiol .05mg
Estrostep	Norethindrone Acetate Ethinyl Estradiol 20mcg 30mcg 35mcg
Ortho Evra	Norelgestromin 150mg Ethinyl Estradiol 20mg
Yasmin	Drospirenone 3mg Ethinyl Estradiol .03mg
Scasonale (nordette)	Levonorgestrel .15mg Ethinyl Estradiol .03mg
Nuva Ring	Etonogestrel 120mg Estradiol 15mcg
Mircette	Desogestrel .015mg Ethinyl Estradiol 20mcg 10mg Fourth Week
LoOvral	Norgestrel .3mg Ethinyl Estradiol 30mcg
Levite	Levonorgestrel .3mg Ethinyl Estradiol 20mcg
Loestrin	Norethindrone Acetate 1mg EE 20mcg
Alesse (Aviane)	Levonorgestrel .1mg EE 20mcg
Tricyclen	Norgestimate .18 .215 .25 EE 35mcg
Orthocyclen	Norgestimate .25mg EE 35mcg

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HORMONE REPLACEMENT THERAPY

PremPro	Conjugated Estrogen/Medroxyprogesterone Acetate
Climara Patch	Estradiol .45ug/day levonorgestrel .015ug/day
Activella	Estradiol 1mg Norethidrone Acetate .05mg
Femhrt	Estradiol .5ug Norethidrone Acetate 1mg
Estratest	Esterified Estrogen/Methyltestosterone Prometrium (Micronized Progesterone)

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ANTIDEPRESSANTS (SSRI)

Effexor	Venlafuxine HCL
Zoloft	Sertraline HCL
Wellbutrin	Bupropion HCL
Serafem	Flouxetine HCL
Paxil	Paroxetine HCL
Lexapro	Escitalopram
Celexa	Citalopram

Matthew Iammatteo M.D. FACOG FACS

The following is a list of patients, drugs used in the study, ages, time frame and outcomes.

Patients	Age	Dates	Drug Combination	Outcomes
EK	25	2004	Tricyclen Low/Zoloft 75mg	Stopped Zoloft 9mo
SC	35	2004	Mircette Serafem 20mg	Moved out of state
LS	40	2002/05	Yasmin Celexa 20mg	Doing well
BB	46	2003/04	Femhrt Effexor 75mg.	Stopped Effexor '04
LM	64	2000/05	Femhrt Zoloft 50mg	doing well
KP	55	2003/05	PremPro.3/1.5 Paxil 25mg	Doing well
LC	39	2001/05	Yasmin Serafem 20mg	Doing well
KA	32	2004/05	Mircette Zoloft 50mg	stopped both > 9 mo.
SR	40	2002/05	Nuvaring Wellbutrin 300mg	Doing well
EL	59	2002/05	Triest 2.5/100 Lexapro10mg	Doing well
BF	59	2004/05	Estragel .06% Effexor 75mg	Doing well
LT	58	2003/05	Prem .3mg Zoloft 100mg	Doing well
DT	40	2003/05	OrthoEvra Celexa.40mg	Doing well
IF	27	2004/05	OrthoEvra Paxil 20mg	Doing well
GM	51	2004/05	Climera .025 Effexor 75mg	Doing well
			Prometrium 100mg	
RM	34	2004/05	Nuvaring Paxil 10 mg	Stopped/ Pregnant
CG	24	2004/05	Loestrin 1.5/30 Paxil 10mg	Doing well
JK	41	2004	Ovcon 1/35 Effexor 75mg	Stopped Effexor '05
FM	26	2004/05	Seasonale Serafem 20mg	Doing well
DM	32	2004/05	Seasonale Wellbutrin 150	Doing well
KS	52	2004	Estring Serafem 20mg	Stopped serafem
SM	47	2003/05	Combipatch 50/140	Doing well
			Effexor 75mg	
HB	32	2003/05	Nuvaring Zoloft 50mg	Doing well
CG	38	2003/05	Yasmin Effexor 75mg	Doing well
OP	33	2004/05	Ovcon 1/35 Serafem 10mg	Doing well
AW	22	2004	Orthocyclen Paxil 12.5mg	stopped paxil
JF	35	2004/05	Nuvaring Zoloft 250mg	Doing well
DH	45	2002/05	Tricyclenlo Lexapro 20mg	Doing well
MW	35	2004/05	Ovcon 1/35 Serafem 20mg	Doing well
MC	40	2004/05	Vivelle.1mg Zoloft 100mg	Doing well
EA	36	2004/05	Levlite Effexor 75mg	Doing well
NS	49	2004/05	Yasmin Lexapro 20mg	Doing well
JR	51	2003/05	climera:05 Prozac 15mg	Doing well
EQ	45	2004/05	Yasmin Serafem 10mg	Stopped serafem
FQ	30	2004/05	Nuvaring Serafem 20mg	Doing well
NP	46	2003/05	Levogestrel Zoloft 25mg	Doing Well
LK	61	2003/05	Estratest Lexapro 25mg	Doing well
HP	31	2005	Estrostep Serafem 20mg	?
MP	32	2003/05	Triphasil Paxil 25mg	Doing well
KL	44	2000/05	Loestrin 1/20mg Lexapro 10	Doing well
DM	41	2002/05	Yasmin Zoloft 50mg	Doing well
BM	42	2003/05	Trilo Zoloft 100mg	Doing well
TT	38	2004/05	Yasmin Effexor 75mg	Doing well

KD	44 2003/05	Cyclen Lexapro 25mg	Stopped OC
HF	63 2001/05	Prem .625mg Effexor 100	Doing well
MS	40 2004/05	Yasmin Serafem 20mg	Doing well
PH	49 2004/05	PremPro.3/1.5 Celexa 20	Doing well
AS	45 2004/05	Mirena Serafem 20mg	Doing well
TC	48 2004/05	Activella Serafem 20mg	Doing well
NZ	35 2002/05	Ovcon35 Paxil 25mg	Doing well
MU	47 1998/05	Estostep Zoloft 10mg	Doing well
LA	75 2003/05	Climera.05 Lexapro 20mg	Doing well
AN	44 2003/05	Estatest.625mg Zoloft100	Doing well
JS	45 2000/05	Yasmin Celexa 20mg	Doing well
AH	37 2004/05	Ovcon35 Prozac10mg	Doing well
MI	38 2002/05	Yasmin Effexor 75mg	Doing well
HT	24 2004/05	Ovcon35 Serafem 10mg	Doing well
DM	35 2003/05	Ovcon35 Serafem 20mg	Doing well
KG	33 2004/05	Ovcon35 Simbalta	Doing well
CC	48 2000/05	Nordette Prozac 20mg	Doing well
AO	40 2001/05	Seasonale Zoloft 100mg	Doing well
CM	35 2001/05	Combipatch50250 Zoloft100	Doing well
JL	39 2002/05	Tricycien lo Prozac 30mg	Doing well
MB	41 27-Jun	Tricycien lo Zoloft 25mg	Trial
ML	55 1996/2005	Prefest Lexapro 20mg	Doing well
RS	55 2004/2005	Climera.05 Prozac10mg	Doing well
LC	38 2003/2005	Yasmin Paxil 25mg	Doing well
SM	39 2003/2005	Alesse Serafem20mg	Doing well
AC	41 2002/2005	Seasonale Prozac 20mg	Doing well
KH	34 2004/2005	Yasmin Zoloft 75mg	Doing well
JL	61 2002/2005	Premarin.3 Celexa 20mg	Doing well
BA	47 2003/2005	Activella Zoloft 100mg	Doing well
KK	36 2004/2005	Alesse Serafem20mg	Doing well
KS	31 2005	Ovcon1/35 Zoloft 50mg	Trial
NM	41 2005	Yasmin Prozac 80mg	Trial
LC	41 2005	Tricyclenlo Paxil 20mg	Trial
GE	45 2005	Yasmin Lexapro 10mg	Trial